



US009408903B2

(12) **United States Patent**
MacAdam

(10) **Patent No.:** **US 9,408,903 B2**
(45) **Date of Patent:** **Aug. 9, 2016**

(54) **VACCINATION METHOD EMPLOYING GENETICALLY STABLE ATTENUATED POLIOVIRUSES COMPRISING MULTIPLE MUTATIONS IN DOMAIN V OF THE 5' NONCODING REGION**

(71) Applicant: **The Secretary of State for Health,**
London (GB)

(72) Inventor: **Andrew MacAdam,** Potters Bar (GB)

(73) Assignee: **The Secretary of State for Health,**
London (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/053,426**

(22) Filed: **Oct. 14, 2013**

(65) **Prior Publication Data**

US 2014/0112952 A1 Apr. 24, 2014

Related U.S. Application Data

(63) Continuation of application No. 12/377,041, filed as application No. PCT/GB2007/003065 on Aug. 10, 2007, now Pat. No. 8,557,252.

(30) **Foreign Application Priority Data**

Aug. 10, 2006 (GB) 0615933.9

(51) **Int. Cl.**

C12N 7/00 (2006.01)

A61K 39/13 (2006.01)

A61K 39/12 (2006.01)

A61K 39/00 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 39/13** (2013.01); **A61K 39/12** (2013.01); **C12N 7/00** (2013.01); **A61K 2039/5254** (2013.01); **C12N 2770/32634** (2013.01); **C12N 2770/32661** (2013.01)

(58) **Field of Classification Search**

CPC **A61K 39/13**; **C12N 7/00**; **C12N 2770/32661**; **C12N 2770/32634**

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

2013/0344108 A1 12/2013 MacAdam

FOREIGN PATENT DOCUMENTS

EP 0 383 433 A1 8/1990
WO 98/41619 A1 9/1998
WO 0007622 A1 2/2000
WO 2012090000 A1 7/2012

OTHER PUBLICATIONS

Rowe, A., et al., 2000, Coding changes in the poliovirus protease 2A compensate for 5'NCR domain V disruptions in a cell-specific manner, *Virology* 269:284-293.*

Dragunsky, E. M., et al., 2004, Evaluation of immunogenicity and protective properties of inactivated poliovirus vaccines: a new surrogate method for predicting vaccine efficacy, *J. Infect. Dis.* 190:1404-1412.*

Combela, N., et al., 2011, Recombination between poliovirus and coxsackie A viruses of species C: a model of viral genetic plasticity and emergence, *Viruses* 3:1460-1484.*

Almond, J., et al., "Approaches to the Construction of New Candidate Poliovirus Type 3 Vaccine Strains," *Developments in Biological Standardization* 78:161-169, 1993.

Girard, M., et al., "Potential Use of Poliovirus as a Vector," *Biologicals* 21(4):371-377, Dec. 1993.

International Search Report mailed Apr. 4, 2012, issued in related International Application No. PCT/GB2011/001779, filed Dec. 29, 2011, 3 pages.

International Preliminary Report on Patentability and Written Opinion mailed Jul. 2, 2013, issued in related International Application No. PCT/GB2011/001779, filed Dec. 29, 2011, 7 pages.

Chumakov, K., et al., "Inactivated Vaccines Based on Alternatives to Wild-Type Seed Virus," *Developments in Biologicals* (Basel) 105:171-177, 2001.

Combela, N., et al., "Recombination Between Poliovirus and Coxsackie A Viruses of Species C: A Model of Viral Genetic Plasticity and Emergence," *Viruses* 3(8):1460-1484, Aug. 2011.

Dragunsky, E., et al., "Transgenic Mice as an Alternative to Monkeys for Neurovirulence Testing of Live Oral Poliovirus Vaccine: Validation by a WHO Collaborative Study," *Bulletin of the World Health Organization* 81(4):251-260, May 2003.

Evans, D.M., et al., "Increased Neurovirulence Associated With a Single Nucleotide Change in a Noncoding Region of the Sabin Type 3 Poliovaccine Genome," *Nature* 314(6011):548-550, Apr. 1985.

Georgescu, M.M., et al., "Mapping of Mutations Contributing to the Temperature Sensitivity of the Sabin 1 Vaccine Strain of Poliovirus," *Journal of Virology* 69(9):5278-5286, Sep. 1995.

Gutiérrez, A.L., et al., "Attenuating Mutations in the Poliovirus 5' Untranslated Region Alter Its Interaction With Polypyrimidine Tract-Binding Protein," *Journal of Virology* 71(5):3826-3833, May 1997.

Holland, J.J., et al., "RNA Virus Populations as Quasispecies," in J.J. Holland (ed.), "Genetic Diversity of RNA Viruses: Current Topics in Microbiology and Immunology," Springer, Berlin, 1992, vol. 176, Chap. 1, pp. 1-20.

La Monica, N., et al., "Mapping of Sequences Required for Mouse Neurovirulence of Poliovirus Type 2 Lansing," *Journal of Virology* 57(2):515-525, Feb. 1986.

MacAdam, A.J., et al., "The 5' Noncoding Region and Virulence of Poliovirus Vaccine Strains," *Trends in Microbiology* 2(11):449-454, Nov. 1994.

MacAdam, A.J., et al., "The 5' Noncoding Region of the Type 2 Poliovirus Vaccine Strain Contains Determinants of Attenuation and Temperature Sensitivity," *Virology* 181(2):451-458, Apr. 1991.

MacAdam, A.J., et al., "Correlation of RNA Secondary Structure and Attenuation of Sabin Vaccine Strains of Poliovirus in Tissue Culture," *Virology* 189(2):415-422, Aug. 1992.

(Continued)

Primary Examiner — Jeffrey Parkin

(74) *Attorney, Agent, or Firm* — Christensen O'Connor Johnson Kindness PLLC

(57) **ABSTRACT**

The invention provides an attenuated poliovirus which does not have a base pair mismatch in stem (a) or (b) of domain V of the 5' non-coding region of its genome, wherein at least seven of the base pairs in stems (a) and (b) are U-A or A-U base pairs.

10 Claims, 10 Drawing Sheets